

Keratoconus: A biomechanical perspective on loss of corneal stiffness

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Keratoconus (KC) is progressive disease of corneal thinning, steepening and collagen degradation. Biomechanics of the cornea is maintained by the intricate collagen network, which is responsible for its unique shape and function. With the disruption of this collagen network, the cornea loses its shape and function, resulting in progressive visual degradation. While KC is essentially a stromal disease, there is evidence that the epithelium undergoes significant thinning similar to the stroma. Several topographical approaches have been developed to detect KC early. However, it is now hypothesized that biomechanical destabilization of the cornea may precede topographic evidence of KC. Biomechanics of KC has been investigated only to a limited extent due to lack of *in vivo* measurement techniques and/or devices. In this review, we focus on recent work performed to characterize the biomechanical characteristics of KC.

Key words: Cornea, crosslinking, keratoconus, modulus

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Keratoconus (KC) is a disease that is characterized clinically by a region of abnormally high curvature, reduced corneal thickness and progressive corneal topographic irregularity. Several causes of KC have been identified, e.g., excessive eye rubbing, systemic diseases, floppy eyelid syndrome, allergies, eczema and genetic. Corneal topography is most widely used to detect KC and several specialized topography based indices to detect KC at different stages of the disease have been summarized in a recent review.^[1] However, these indices do not have the same detection power in subclinical or early KC corneas.^[1] Corneal biomechanics has the potential to bridge the gap existing in detection of subclinical KC.^[1-3]

Structural Features of Keratoconus

X-ray diffraction studies of KC corneas have shown that the native collagen fiber network is mostly disorganized and lacks the preferred directions and symmetry, although no significant changes are seen in the packing of collagen fibers that may lead to corneal thinning.^[4] Biochemical studies have shown similar collagen composition distribution among both normal and KC corneas, although an increase in collagenolysis, loss of keratocytes and reduced collagen cross-links were also observed in KC corneas. It has been proposed that KC progression is characterized by a biomechanical cycle of decompensation with thinning, increasing strain and redistribution of stress and that the cycle is initiated by a focal reduction of material properties. Some of the early work on KC has focused on traditional mechanical (*ex vivo*) testing of KC tissue samples from donor human eyes. *Ex vivo* testing has clearly demonstrated the

mechanical weakening of the stroma compared with normal corneas.^[5] Several biomechanical models have been proposed to describe the topographic changes in the cornea as a result of collagen degradation in KC though no direct *in vivo* measurement of collagen distribution in corneas exist today to validate these models.^[6,7] These models describe KC as a regional or localized weakness in the cornea, with virtually non-existing collagen orientation and distribution compared with normal corneas. Specifically, Roy and Dupps^[7] have also adapted their model to describe biomechanical changes in KC corneas after collagen crosslinking, which is one of the promising therapies for KC.

Biomechanics of KC: Clinical Diagnosis Tools

In vivo measurement of KC biomechanics is a difficult task and available modalities are summarized below.

Ocular response analyzer

The ORA was the first device introduced to measure biomechanical features of the cornea.^[2,3] The ORA reports two indices: Corneal hysteresis (CH) and corneal resistance factor (CRF). CH is considered to be a measure of corneal viscoelasticity. CRF has been formulated to delineate the effect of central corneal thickness (CCT) on CH. Both CH and CRF decrease in KC corneas compared with normal patients, which indicates mechanical weakening of the stroma.^[1,8] However, similar changes in CH and CRF are also observed in biomechanically inferior corneas such as after refractive surgery, ectasia. Thus, the ORA needs to be complemented with other diagnostic imaging tools to obtain a reliable diagnosis of KC. Further, the exact correlation of CH and CRF to true measures of corneal mechanical properties, e.g., Young's modulus, is still unknown.^[1,8] Waveform analysis of ORA applanation signal, shows some promise of providing additional information about the biomechanical status of KC cornea,^[9] but has not been validated in a larger population.

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Corvis-ST

Recently a new *in vivo* device known as the Corvis-ST (Oculus Optikgeräte GmbH, Germany) has been introduced for measurement of intraocular pressure, central corneal thickness and corneal biomechanics.^[8] The device uses applanation of the cornea with a high-pressure air pulse to deform it and records corneal deformation at the apex from continuously recorded Scheimpflug images. The device reports the maximum displacement of the cornea and this could be used as a surrogate measure of corneal stiffness similar to CH. The usefulness of the device to gauge KC severity and diagnose subclinical KC is yet to be proven. However, the Corvis-ST is equipped with a high-speed camera capable of taking 2-dimensional images of a cross-section of the cornea during its deformation, which can possibly yield additional metrics about the biomechanical status of the cornea.

Shear wave propagation imaging

Supersonic shear imaging is another promising imaging technique for rapid evaluation of the corneal stiffness.^[10] This method generates shear waves in the anterior stroma using focused ultrasound and the speed of propagation of the shear waves in the stroma is measured. Using linear elastic theory, the speed of the wave can be converted to shear and Young's modulus. Recently this method has also been used to measure the biomechanics of the cornea after collagen crosslinking where the stiffness of the stroma increases.^[10]

Optical coherence tomography

Another method utilizes OCT to measure the biomechanical properties of the cornea.^[9] This method uses physical perturbation of the cornea to induce strains in the stroma accompanied by real-time OCT imaging of the deformed configuration of the cornea. By using a cross-correlation algorithm, the deformations in the stroma can be measured. The advantage of this method is that it enjoys the maximum spatial resolution within the stroma among all techniques. Thus focused variations in the corneal biomechanical properties in KC may be better detected with this technology.

Understanding of the biomechanics of the KC is critical for its diagnosis and therapy. Presently, biomechanical stabilization through collagen crosslinking or corneal transplantation is the only way to treat the disease. With the evolution of advanced

imaging methods for biomechanical evaluation, patient-specific customized treatment protocols could be developed.

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